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 NEWS 13  JUl 14  FSTA enhanced with Japanese patents
 NEWS 14  JUl 19  Coverage of Research Disclosure reinstated in DWPI
 NEWS 15  AUG 09  INSPEC enhanced with 1898-1968 archive
 NEWS 16  AUG 28  ADISCTI Reloaded and Enhanced
 NEWS 17  AUG 30  CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS 18  SEP 11  CA/CAplus enhanced with more pre-1907 records

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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FILE 'HOME' ENTERED AT 08:50:00 ON 14 SEP 2006

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FILE LAST UPDATED:          13 SEP 2006      <20060913/UP>
MOST RECENT UPDATE WEEK:        200636        <200636/EW>
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=> s CPT-11 or CPT11 or CPT () 11
          2966 CPT
            90 CPTS
          3003 CPT
                 (CPT OR CPTS)
        834457 11
           473 CPT-11
                 (CPT(W)11)
            22 CPT11
          2966 CPT
            90 CPTS
          3003 CPT
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              (CPT OR CPTS)
         834457 11
            473 CPT (W) 11
L1          486 CPT-11 OR CPT11 OR CPT (W) 11

=> s pretarget?
L2          641 PRETARGET?

=> s l1 and l2
L3           17 L1 AND L2

=> s l3 not py>1998
         791952 PY>1998
L4            1 L3 NOT PY>1998

=> d ibib 1

L4     ANSWER 1 OF 1      PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        1997041898 PCTFULL  ED 20020514
TITLE (ENGLISH):         TARGETED COMBINATION IMMUNOTHERAPY OF CANCER
TITLE (FRENCH):          IMMUNOTHERAPIE-CIBLE ASSOCIEE CONTRE LE CANCER
INVENTOR(S):             GRIFFITHS, Gary, L.;
                         HANSEN, Hans, J.
PATENT ASSIGNEE(S):      IMMUNOMEDICS, INC.;
                         GRIFFITHS, Gary, L.;
                         HANSEN, Hans, J.
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER             KIND     DATE
                         --------------------------------
                         WO 9741898           A1 19971113
DESIGNATED STATES
       W:                AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
                         ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS
                         LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG
                         SI SK TJ TM TR TT UA UG US UZ VN YU GH KE LS MW SD SZ
                         UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR
                         GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML
                         MR NE SN TD TG
APPLICATION INFO.:       WO 1997-US7395       A  19970502
PRIORITY INFO.:          US 1996-60/017,011      19960503

=> d kwic

L4     ANSWER 1 OF 1      PCTFULL   COPYRIGHT 2006 Univentio on STN

DETD  . . .  converted to the active metabolite which kills the
       tumor. Examples of such enzyme-prodrug binding partners
       are I antibody-carboxypeptidase G2 and topoisomerase-
       inhibiting prodrug CPT-11; beta-lactamase and
       cephalosporin-doxorubicin; alkaline phosphatase and
       etoposide phosphate; carboxypeptidase G2 and glutamic
       acid derivative of benzoic acid mustard; and beta-
       glucuronidase and the glucuronide.  .  .

       5,525,338, herein incorporated in its entirety by
       reference, discloses the use of secondary targeted
       antibodies within pretargeting protocols. In this
       embodiment, the use of biotin-avidin recognition is
       supplemented by antibody(3) recognition of the same or a
       different epitope on the.  .  .
```

```
=> s antibody (2W) enzyme
         77341 ANTIBODY
         76760 ANTIBODIES
         91010 ANTIBODY
                 (ANTIBODY OR ANTIBODIES)
        108842 ENZYME
         91174 ENZYMES
        128660 ENZYME
                 (ENZYME OR ENZYMES)
L5        6489 ANTIBODY (2W) ENZYME

=> d his

     (FILE 'HOME' ENTERED AT 08:50:00 ON 14 SEP 2006)

     FILE 'PCTFULL' ENTERED AT 08:50:13 ON 14 SEP 2006
L1          486 S CPT-11 OR CPT11 OR CPT () 11
L2          641 S PRETARGET?
L3           17 S L1 AND L2
L4            1 S L3 NOT PY>1998
L5         6489 S ANTIBODY (2W) ENZYME

=> s l5 and l1
L6           31 L5 AND L1

=> s l6 not py>1998
        791952 PY>1998
L7            0 L6 NOT PY>1998

=> d kwic l6

L6     ANSWER 1 OF 31    PCTFULL   COPYRIGHT 2006 Univentio on STN

DETD  . . .  (TELCYTATM);
       acetogenins (especially bullatacin and bullatacinone); delta
       tetrahydrocannabinol (dronabinol, MARINOLO);
       beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin
       (including the synthetic analogue
       topotecan (HYCAMTINID), CPT-11 (irinotecan,
       CAMPTOSARO), acetylcamptothecin, scopolectin, and 9-
       aminocamptothecin); bryostatin; callystatin; CC-1065 (including its
       adozelesin, carzelesin and bizelesin
       synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide;.
       . .
  . . .
       to a cytotoxic polypeptide. Other insertional variants of the antibody
       molecule include the fusion to the N- or C-terminus of the
       antibody to an enzyme (e.g. for ADEPT) or a
       polypeptide which increases the serum half-life of the antibody.


=> s antibody (3W) enzyme
         77341 ANTIBODY
         76760 ANTIBODIES
         91010 ANTIBODY
                 (ANTIBODY OR ANTIBODIES)
        108842 ENZYME
         91174 ENZYMES
        128660 ENZYME
                 (ENZYME OR ENZYMES)
L8        8842 ANTIBODY (3W) ENZYME

=> s l8 and l1
L9           42 L8 AND L1
```

```
=> s l9 not py>1998
        791952 PY>1998
L10          0 L9 NOT PY>1998

=> s enzyme (3W) antibod?
        108842 ENZYME
         91174 ENZYMES
        128660 ENZYME
                 (ENZYME OR ENZYMES)
         91058 ANTIBOD?
L11       7359 ENZYME (3W) ANTIBOD?

=> s l11 and l1
L12         31 L11 AND L1

=> s l12 not py>1999
        724392 PY>1999
L13          1 L12 NOT PY>1999

=> d kwic

L13    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN

DETD   Structure-Based Classes
       1. Fluoropyrimidines
       2. Pyrimidine Nucleosides
       3. Purines
       4. Platinum Analogues
       5. Anthracyclines/Anthracenediones
       6. Podophyllotoxins
       7. Camptothecins
       B. Hormones and Hormonal Analogues
       9. Enzymes, Proteins and Antibodies
       10. Vinca Alkaloids
       11. Taxanes
       Mechanism-Based Classes
       1. Antihormonals
       2. Antifolates
       4
       . Antimicrotubule Agents
       4. Alkylating Agents (Classical and Non-Classical)
       5. Antimetabolites
       6. Antibiotics
       7. Topoisomerase Inhibitors
       8. Antivirals
       9. Miscellaneous Cytotoxic.  .  .
  .  .  .
       103;
       8. Hormones and Hormonal Analogues- Diethylstilbestrol,
       Tamoxifen, Toremefine, Tolmudex, Thymitaq, Flutamide,
       Bicalutamide, Finasteride, Estradiol, Trioxifene,
       Droloxifene, Medroxyprogesterone Acetate, Megesterol Acetate,
       Aminoglutethimide, Testolactone and others;
       9. Enzymes, Proteins and Antibodies- Asparaginase,
       Interleukins, Interferons, Leuprolide, Pegaspargase, and
       others;
       10. Vinca Alkaloids- Vincristine, Vinblastine,
       Vinorelbine, Vindesine;
       11. Taxanes- Paclitaxel, Docetaxel, and others.
  .  .  .
       since this discovery to
       developing water soluble camptothecin derivatives which
       remained in their active lactone form. Along these lines, the
       25
       recently approved Irinotecan (CPT-11) and Topotecan
```

```
       were
       developed. Irinotecan is a water soluble prodrug of the
       highly active, highly lipophilic derivative of CPT known as
       SN38 (10-hydroxy. . .


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     (FILE 'HOME' ENTERED AT 08:50:00 ON 14 SEP 2006)

     FILE 'PCTFULL' ENTERED AT 08:50:13 ON 14 SEP 2006
L1            486 S CPT-11 OR CPT11 OR CPT () 11
L2            641 S PRETARGET?
L3             17 S L1 AND L2
L4              1 S L3 NOT PY>1998
L5           6489 S ANTIBODY (2W) ENZYME
L6             31 S L5 AND L1
L7              0 S L6 NOT PY>1998
L8           8842 S ANTIBODY (3W) ENZYME
L9             42 S L8 AND L1
L10             0 S L9 NOT PY>1998
L11          7359 S ENZYME (3W) ANTIBOD?
L12            31 S L11 AND L1
L13             1 S L12 NOT PY>1999

=> s antibod? (3W) enzyme
         91058 ANTIBOD?
        108842 ENZYME
         91174 ENZYMES
        128660 ENZYME
                 (ENZYME OR ENZYMES)
L14       8855 ANTIBOD? (3W) ENZYME

=> s l14 and l1
L15            42 L14 AND L1

=> s l15 not py>1999
        724392 PY>1999
L16             1 L15 NOT PY>1999

=> d ibib kwic

L16    ANSWER 1 OF 1      PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        1999042593 PCTFULL  ED 20020515
TITLE (ENGLISH):         COMPOSITIONS AND METHODS FOR SENSITIZING AND INHIBITING
                         GROWTH OF HUMAN TUMOR CELLS
TITLE (FRENCH):          COMPOSITIONS ET PROCEDES SERVANT A SENSIBILISER ET A
                         INHIBER LA CROISSANCE DE CELLULES CANCEREUSES HUMAINES
INVENTOR(S):             DANKS, Mary, K.;
                         POTTER, Philip, M.;
                         HOUGHTON, Peter, J.
PATENT ASSIGNEE(S):      ST. JUDE CHILDREN'S RESEARCH HOSPITAL;
                         DANKS, Mary, K.;
                         POTTER, Philip, M.;
                         HOUGHTON, Peter, J.
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER             KIND     DATE
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                         WO 9942593          A1 19990826
DESIGNATED STATES
      W:                 AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
                         ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
                         KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT
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ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ
TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT
SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-US3171 A 19990212
PRIORITY INFO.: US 1998-60/075,258 19980219

DETD CPT-11 (irinotecan, 7-ethyl [4-(1-piperidino) piperidinolcarbonyloxycamptothecin) is a prodrug currently under investigation for the treatment of cancer that is converted to the active drug. . .

5 49:5077-5082). The specific enzyme responsible for activation in vivo of CPT-11 has not been identified, although serum or liver homogenates from several mammalian species have been shown to contain activities that convert CPT-11 to SN-38 (Tsuji, T. et al. 1991. J. Pharmacobiol. D_ynamics 14:341-349; Senter, P.D. et al. 1996. Cancer Res. 56:1471-1474; Satoh, T.

In fact, SN-38 can be detected in the plasma of animals and humans minutes after the administration of CPT-11 (Stewart, C.F. et al. 1997. Cancer Chemother. Pharmacol. 40:259-265; Kaneda, N. et al. 1990. Cancer Res. 50:1715-1720; Rowinsky, E.K. et al. 1994. Cancer. . .

. . . of this class of enzymes has yet to be identified. A recent biochemical analysis of 13 CEs compared their ability to metabolize CPT-11 to SN While the efficiency of conversion varied between enzymes, those isolated from rodents were the most efficient (Satoh, T. et al. 1994.. . .

. . . EMBL databases, including a rat serum and rat liver microsomal CE. Interestingly, CEs purified from human tissues demonstrated the least efficient conversion of CPT-11 to SN-38, with less than 5% of the prodrug being 5 converted to active drug (Leinweber, F.J. 1987. Drug Metab.

In addition to metabolism to SN-38, in humans CPT-11 is also metabolized to a compound known as APC (Haaz, M.C. et al.

In preclinical studies, CPT-11 administered to immune-deprived mice bearing human tumor xenografts produces complete regression of glioblastomas, rhabdomyosarcomas (RMS)j, neuroblastomas, and colon adenocarcinomas (Houghton, P.J. et al. 1995. Cancer Chemother. Pharmacol. 36:393-403; Houghton, P.J.. et al. 1993. Cancer Res. 53:2823-2829). However, maintenance of tumor regression in studies with CPT-11 appears to be dependent upon drug scheduling, suggesting that viable tumor cells survive therapy (i.e., minimal residual disease (MRD)). These studies also showed a steep dose-response relationship between dose of drug administered and induction of tumor regression. For example, 20 mg of CPT-11 /kg/day given daily for 5 days for two weeks produced complete regressions of Rh18 RMS xenografts, while 10 mg/kg/day given on the same schedule. . .

Similar effects were seen when mice bearing SJGC3A colon adenocarcinoma xenografts were treated with 40 mg CPT-11/kg compared to a 20 mg/kg dose.

Early clinical trials with CPT-11 indicate that the prodrug also has anti-tumor activity in vivo against many different types of solid tumors in humans. However, myelosuppression and secretory. . .

. . . present invention, polynucleotides encoding a carboxylesterase enzyme or active fragments thereof and polypeptides encoded thereby which are capable of metabolizing the chemotherapeutic prodrug CPT-11 and its inactive metabolite APC to active drug SN-38 are disclosed. Use of this enzyme in combination with APC renders this inactive metabolite. . . invention and a disease-specific responsive promoter can be delivered to selected tumor cells to sensitize the tumor cells to the chemotherapeutic prodrug CPT-11, 30 thereby inhibiting tumor cell growth.

Figure 5 is a linegraph comparing % cell survival, depicted on the Y-axis, at various concentrations of CPT-11, 30 depicted on the X-axis. Control Cos7 cells (filled squares) are approximately 350-fold more sensitive to CPT-11 than Cos7 cell transfected with CE (filled triangles).

Figure 8 provides the chemical structures of CPT-11, APC and SN

Figure 9A. 9B, and 9C are linegraphs showing the responses of mice bearing Rh30 and RhHpIRESI.bbit rhabdosarcoma xenografts to CPT-11 treatment. Each line on each graph shows the growth of an individual tumor. The tumor growth rate is depicted on the Y-axis. . .

. . . depicts cells expressing rabbit CE (RhHpIRESabbit) not treated with CPT Figure 9B depicts cells expressing rabbit CE (RhHpIRES,abbit) and then treated with CPT-11 and shows complete tumor regression, even out to 12 weeks. Figure 9C depicts control cells (Rh30) exposed to CPT-11 and shows initial regression but regrowth.

Figure 10 is a linegraph showing the effects of CPT-11 treatment on U373 glioblastoma xenografts expressing rabbit CE. Mice bearing xenografts were treated with CPT-11 (7.5 mg/kg for 5 days) for three treatment cycles. The tumor growth rate is depicted on the Y-axis in terms of tumor. . .

Detailed Descri-ption of the Invention

CPT-11 is a promising anti-cancer prodrug, that when given to patients, is converted to its active metabolite SN-38 by a human carboxylesterase. However,. . .

. . . to compositions comprising a polynucleotide of the present invention which

have been found to be useful in sensitizing tumor cells to CPT-11 cytotoxicity by combination therapy of the prodrug and a CE enzyme. The present invention thus provides methods for sensitizing tumor cells to. . .

. . . In addition, the rabbit CE demonstrated greater than 85% homology with human alveolar macrophage CE yet the latter enzyme failed to convert CPT-11 to SN-38 in mammalian cells. This indicates that while CEs may have a broad range of substrate specificities, the efficiency with which similar. . .

. . . the SV40 origin of replication allowing plasmid amplification in cells expressing the large T antigen, such as Cos7. The IC5. value for CPT-11 for cells expressing the CE was approximately B-80 fold, and most typically about 56 fold, less than that of the parent cell line thus indicating 35 that the enzyme has sensitized mammalian cells to CPT-11 (see Figure 5).

. . . to sensitize the tumor cells to a chemotherapeutic prodrug. The ability of the combination of a rabbit CE of the present invention and CPT-11 to sensitize human tumor cells to CPT-11 was examined. Experiments were first performed to confirm that the metabolite produced by the activity of a CE of the present invention is. . .

. . . to 5 units of CE that had been inactivated by heating produced no inhibition of cell growth. In contrast, reaction products of CPT-11 incubated with 1 to 5 units of active CE produced a 30-60% inhibition of cell growth. These data are consistent with the conversion of CPT-11 to SN-38 by CE in these cells.

The CE activity of extracts of the transfected cells was then determined. The IC511 values for CPT-11 in Rh30 rhabdomyosarcoma cells that had been stably transfected with a rabbit liver CE cDNA of the present invention or the pIRES vector. . . alone were also determined. Cells transfected with the CE cDNA contained approximately 60-fold more CE activity than control cells. The IC50 Of CPT-11 for Rh30pIRES cells (no CE cDNA) was 4.33 X 10-6 M while the IC50 for the Rh30pIRES.,bbit cells was 5.76 X 10-7. . . M. Therefore, the transfected cells were more than 8-fold more sensitive to CPT These data are consistent with an increased conversion of CPT-11 to SN-38 in 35 the cells transfected with a CE of the present invention.

. . . CE of the present 5invention. These data confirm the unique ability of a CE of the present invention to activate the prodrug CPT-11 , as well as to activate one of its metabolites. Further, experiments in U-373 cells that express a CE of the present invention showed. . .

In vivo efficacy of the CE of the present invention to

sensitize tumor cells to CPT-11 has also been demonstrated in two different types of tumor cells. Experiments conducted in a mouse model demonstrate that a CE of. . . for rabbit CE was maintained for at least 12 weeks. Importantly, tumors were advanced (greater than 1 CM3 in volume) before treatment with CPT-11 began. As depicted in Figure 9B, tumors in mice expressing CE and treated with 2.5 mg CPT-11 /kg/day for five days each week for two weeks (one cycle of therapy), repeated every 21 days for a total of three. . . not regrow during the 12 weeks of the study. In contrast, tumors that did not express the CE regressed only transiently with CPT-11 treatment, with regrowth occurring within one week after CPT-11 treatment stopped (see Figure 9C).

. . .

In a second set of experiments, human U373 glioblastoma xenografts that express rabbit liver CE were shown to be more sensitive to CPT-11 than xenografts transfected with a control plasmid (no rabbit CE). Xenografts established from cells

- 22

transfected with the plasmid encoding rabbit. . .

Thus, these data support the use of the combination of polynucleotide encoding a CE of the present invention and CPT-11 to reduce the amount of CPT-11 needed to produce inhibition of tumor cell growth, or to sensitize the tumor cells to CPT-11. These data also support the use of the present invention to allow for decreased dosage with CPT-11 in cancer patients, thus reducing the likelihood of dose-limiting toxicity.

. . .

promoter. The vectors can then be injected into the site of tumor removal along with systemic administration of a prodrug such as CPT-11 to inhibit the recurrence of tumors due to residual tumor cells present after surgical resection of a tumor.

Another method for delivering CEs to selected tumor cells involves antibody direct enzyme prodrug therapy (ADEPT).

. . .

a molecule such as rabbit liver CE. Cellular internalization of the complex and release of active CE would be achieved, leading to CPT-11 activation that is specific for cells expressing the marker antigen.

Both the secreted and the endoplasmic reticulum-localized protein can convert CPT-11 to SN-38; therefore, the potential exists for a bystander effect from cells expressing the secreted enzyme. A similar bystander effect has been demonstrated. . .

Extracellular activation of CPT-11 may result in more efficient eradication of MRD in that uninfected neighboring

tumor cells would be killed by exogenously produced SN Gene therapy protocols with a secreted CE in combination with CPT-11 may therefore be more appropriate for the elimination of residual tumor tissue. Accordingly, in this embodiment,

- 24 -

it may be preferred. . . .

. . .

the plasma. Attachment of a CE of the present invention to the cell surface should result in local extracellular activation of CPT-11 to SN-38 and enhance local cell kill. Purging bone marrow of contaminating tumor cells will be accomplished by an intracellular enzyme, whereas eradication of MRD is better achieved by an enzyme that activates CPT-11 at an extracellular location.

CEs of the present invention cleave the COOC bond present as an ester linkage in CPT-11 to generate SN-38 (see Figure 8). Since this enzyme may also catalyze the activation of other compounds that contain such a linkage,. . . .

EXAMPLES

Example 1: Identification of CEs

A CE enzyme suitable for converting CPT-11 to the active form, SN-38 was identified by testing a variety of samples.

. . .

CEs were commercially available, several of these were also tested for their ability to metabolize CPT Both rabbit and pig liver CEs metabolized CPT-11 efficiently. The commercially available pig CE contained several proteins. However, the major bands were very similar in molecular weight and did not. . . .

. . .

activity of rabbit CE

The in vitro activity of rabbit liver CE was examined in tumor cell lines. The growth inhibition of CPT-11 was compared in cells with and without active rabbit CE. The cells used were Rh30 cells (lo') that had been electroporated with 20. . . .

In the first assay, CPT-11 was pre-incubated with rabbit liver CE to produce SN-38 prior to exposure of the cells to drug. specifically, 0.5 to 5 units of CE were incubated with 1 yM CPT-11 at 370C in DMEM medium for 2 hours. Each reaction mixture was then filter-sterilized and Rh3o cells were exposed to drug for. . . was replaced with drug-free medium containing serum. Enzyme that had been inactivated by boiling for five minutes prior to incubation with drug or CPT-11 to which no enzyme had been added were used as negative controls. Cells were allowed to grow for 3 cell doubling times. . . .

. . .

the conversion of o-nitrophenyl acetate to o-nitrophenol. Further, the Rh30pIRES cells transfected with rabbit CE were greater than 8-fold more sensitive to CPT-11 than controls, as shown by a decrease in the IC,, values.

Therefore, Rh30 cells stably transfected with rabbit CE were more sensitive to growth inhibition by CPT-11 than cells that did not contain the cDNA for rabbit CE.

- 30 -

Example 5: Rabbit CE activates APC, a novel prodrug

In addition to efficiently converting CPT-11 to the active compound SN-38, experiments were also performed demonstrating the ability of rabbit liver CE to convert the 5inactive metabolic end product. . .

. . .

in the prevention of MRD. In this model, treatment of immune-deprived mice, i.e., SCID mice, bearing human NB-1691 xenografts with 10 mg/kg CPT-11 daily for 5 days on two consecutive weeks results in complete regression of the tumor. However, within 4-6 weeks, tumors are palpable. . .

. . .

identical fashion with Rh30 cells not transfected with the plasmid. When the tumors reached a size of approximately 1 cm', 2.5 mg CPT-11/kg/day was administered five days each week for two weeks (one cycle of therapy), repeated every 21 days for a total of three. . .

In contrast, tumors not expressing the CE regressed only transiently,, regrowing within one week after CPT-11 treatment had stopped (Figure 9C).

Cells were injected subcutaneously into the flanks of the SCID mice. When tumors reached approximately 1 CM3 in size, CPT-11 was administered daily for five days each week as described above, for three cycles, at a dose of 7.5 mg/kg/day.

. . .

implantation in this model during the 4 to week period when tumors are not present, followed by treatment with low doses of CPT-11, also demonstrates the effectiveness of the virus at preventing MRD. Typically, 5 since tumor regression is complete 3 weeks after commencing treatment with CPT-11, adenovirus/drug administration begins at week 4. In initial experiments, adenovirus is administered on Monday, Wednesday, Friday and CPT-11 is given daily on Tuesday through Saturday for two cycles. This permits determination of the most tolerated, effective schedule and dosage of adenovirus and CPT-11 administration to produce the longest delay of recurrent disease. These results are used to determine correct dosage for treatment of human MRD.. . .

. . .

bone marrow of these same animals contains neuroblastoma cells. The success of ex vivo purging of bone marrow with the rabbit liver CE/CPT-11 combination is demonstrated by transplanting purged bone marrow into lethally irradiated mice. If mice remain disease free for extended periods of time, this. . .

Example 8: Treatment of Minimal Residual Disease (MRD) in humans
The rabbit CE in combination with CPT-11 or other prodrugs activated by 'this enzyme is used to purge bone marrow 5of residual tumor cells prior to autologous bone marrow transplants. . .

Nature Med. 3:639-645). CPT-11 is administered over the next
one to six weeks to elicit tumor selective cell kill. Doses 20 and schedules of CPT-11 are determined in clinical trials of
CPT-11 by itself and in human xenograft model systems to
produce maximal tumor effect.
. . .
majority of hematopoietic progenitor cells. Two days
- 34 -
following adenoviral transduction, cells are exposed for two hours to a range of CPT-11 concentrations, usually varying
from 50 nM to 100 pM. Two days after exposure to drug, the marrow sample is harvested and stored. . .

CLMEN 13 The method of claim 12 wherein the chemotherapeutic prodrug is selected from a group consisting of CPT-11 and APC.

15 The method of claim 14 wherein the chemotherapeutic prodrug is selected from a group consisting of CPT-11 and APC.

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	15.57	15.78

FILE 'CAPLUS' ENTERED AT 08:55:25 ON 14 SEP 2006
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FILE COVERS 1907 - 14 Sep 2006 VOL 145 ISS 12
FILE LAST UPDATED: 13 Sep 2006 (20060913/ED)

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=> s antibod? (3W) enzyme
470877 ANTIBOD?
783759 ENZYME

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        454161 ENZYMES
        992426 ENZYME
                 (ENZYME OR ENZYMES)
L17       6081 ANTIBOD? (3W) ENZYME

=> s CPT-11/cn
   REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
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L19          0 L18

=> s CPT11/cn
   REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.




L21          0 L20

=> s cpt 11/cn\
'CN\' IS NOT A VALID FIELD CODE
L22          0 CPT 11/CN\

=> s cpt 11/cn
   REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.




L24        888 L23

=> d his

     (FILE 'HOME' ENTERED AT 08:50:00 ON 14 SEP 2006)

     FILE 'PCTFULL' ENTERED AT 08:50:13 ON 14 SEP 2006
L1          486 S CPT-11 OR CPT11 OR CPT () 11
L2          641 S PRETARGET?
L3           17 S L1 AND L2
L4            1 S L3 NOT PY>1998
L5         6489 S ANTIBODY (2W) ENZYME
L6           31 S L5 AND L1
L7            0 S L6 NOT PY>1998
L8         8842 S ANTIBODY (3W) ENZYME
L9           42 S L8 AND L1
L10           0 S L9 NOT PY>1998
L11        7359 S ENZYME (3W) ANTIBOD?
L12          31 S L11 AND L1
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L13            1 S L12 NOT PY>1999
L14         8855 S ANTIBOD? (3W) ENZYME
L15           42 S L14 AND L1
L16            1 S L15 NOT PY>1999

     FILE 'CAPLUS' ENTERED AT 08:55:25 ON 14 SEP 2006
L17         6081 S ANTIBOD? (3W) ENZYME
                 S CPT-11/CN

     FILE 'REGISTRY' ENTERED AT 08:55:50 ON 14 SEP 2006
L18            0 S CPT-11/CN

     FILE 'CAPLUS' ENTERED AT 08:55:51 ON 14 SEP 2006
L19            0 S L18
                 S CPT11/CN

     FILE 'REGISTRY' ENTERED AT 08:55:58 ON 14 SEP 2006
L20            0 S CPT11/CN

     FILE 'CAPLUS' ENTERED AT 08:55:59 ON 14 SEP 2006
L21            0 S L20
L22            0 S CPT 11/CN\
                 S CPT 11/CN

     FILE 'REGISTRY' ENTERED AT 08:56:12 ON 14 SEP 2006
L23            1 S CPT 11/CN

     FILE 'CAPLUS' ENTERED AT 08:56:12 ON 14 SEP 2006
L24          888 S L23

=> s l24 and l17
L25            7 L24 AND L17

=> s l17 (L) l24
L26            1 L17 (L) L24

=> d ibib

L26  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2002:236399  CAPLUS
DOCUMENT NUMBER:          136:268117
TITLE:                    Antibody-enzyme conjugates for increasing the
                          target-specific toxicity of a chemotherapy drug
INVENTOR(S):              Griffiths, Gary L.; Hansen, Hans J.
PATENT ASSIGNEE(S):       Immunomedics, Inc., USA
SOURCE:                   U.S., 8 pp.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    -------------------    --------
     US 6361774           B1    20020326    US 1999-399221         19990917
     US 2002114808        A1    20020822    US 2002-66782          20020206
PRIORITY APPLN. INFO.:                      US 1998-101039P     P  19980918
                                            US 1999-399221      A3 19990917
REFERENCE COUNT:          32    THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d l25 ibib 1-7

L25  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
```

ACCESSION NUMBER: 2005:546856 CAPLUS
DOCUMENT NUMBER: 143:73869
TITLE: Design and sequences of human butyrylcholinesterase variants that alter the activity of anticancer agents and the use in cancer treatment
INVENTOR(S): Watkins, Jeffry D.; Pancook, James D.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 60 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005136044	A1	20050623	US 2003-728723	20031204
PRIORITY APPLN. INFO.:			US 2003-728723	20031204

L25 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:817401 CAPLUS
DOCUMENT NUMBER: 141:289026
TITLE: Rabbit liver carboxylesterase capable of activating chemotherapeutic prodrug and thereby sensitizing and inhibiting growth of human tumor cells
INVENTOR(S): Danks, Mary K.; Potter, Philip M.; Houghton, Peter J.
PATENT ASSIGNEE(S): St. Jude Children's Research Hospital, USA
SOURCE: U.S., 39 pp., Cont.-in-part of WO 99 42,593.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6800483	B1	20041005	US 2000-595682	20000616
WO 9942593	A1	19990826	WO 1999-US3171	19990212

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004259829	A1	20041223	US 2004-858271	20040601
PRIORITY APPLN. INFO.:			US 1998-75258P	P 19980219
			WO 1999-US3171	A2 19990212
			US 2000-595682	A1 20000616

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:453053 CAPLUS
DOCUMENT NUMBER: 141:1228
TITLE: Use of multi-specific, non-covalent complexes for targeted delivery of therapeutics
INVENTOR(S): Griffiths, Gary L.; Govindan, Serengulam V.; Hansen, Hans J.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA; McCall, John Douglas
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004045642	A1	20040603	WO 2003-GB4994	20031117
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2505717	AA	20040603	CA 2003-2505717	20031117
AU 2003283599	A1	20040615	AU 2003-283599	20031117
US 2004166115	A1	20040826	US 2003-714391	20031117
EP 1560596	A1	20050810	EP 2003-775576	20031117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006514627	T2	20060511	JP 2004-552884	20031117
PRIORITY APPLN. INFO.:			US 2002-426379P P	20021115
			WO 2003-GB4994 W	20031117

L25 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:584407 CAPLUS
DOCUMENT NUMBER: 139:358244
TITLE: Carboxylesterase-mediated sensitization of human tumor cells to CPT-11 cannot override ABCG2-mediated drug resistance
AUTHOR(S): Wierdl, Monika; Wall, Amelia; Morton, Christopher L.; Sampath, Janardhan; Danks, Mary K.; Schuetz, John D.; Potter, Philip M.
CORPORATE SOURCE: Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, USA
SOURCE: Molecular Pharmacology (2003), 64(2), 279-288
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:236399 CAPLUS
DOCUMENT NUMBER: 136:268117
TITLE: Antibody-enzyme conjugates for increasing the target-specific toxicity of a chemotherapy drug
INVENTOR(S): Griffiths, Gary L.; Hansen, Hans J.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S., 8 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6361774	B1	20020326	US 1999-399221	19990917
US 2002114808	A1	20020822	US 2002-66782	20020206

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PRIORITY APPLN. INFO.:                         US 1998-101039P     P  19980918
                                               US 1999-399221      A3 19990917
REFERENCE COUNT:          32     THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
                                 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25  ANSWER 6 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1999:549389  CAPLUS
DOCUMENT NUMBER:          131:165300
TITLE:                    Rabbit liver carboxylesterase capable of activating
                          chemotherapeutic prodrug and thereby sensitizing and
                          inhibiting growth of human tumor cells
INVENTOR(S):              Danks, Mary K.; Potter, Philip M.; Houghton, Peter J.
PATENT ASSIGNEE(S):       St. Jude Children's Research Hospital, USA
SOURCE:                   PCT Int. Appl., 70 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
     WO 9942593           A1    19990826    WO 1999-US3171         19990212
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             DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
             MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
             TR, TT, UA, UG, US, UZ, VN, YU, ZW
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CA 2320808           AA    19990826    CA 1999-2320808        19990212
     AU 9928679           A1    19990906    AU 1999-28679          19990212
     AU 755251            B2    20021205
     EP 1054979           A1    20001129    EP 1999-909488         19990212
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
     JP 2002504340        T2    20020212    JP 2000-532533         19990212
     US 6800483           B1    20041005    US 2000-595682         20000616
     US 7018631           B1    20060328    US 2000-622568         20000831
     US 2004259829        A1    20041223    US 2004-858271         20040601
PRIORITY APPLN. INFO.:                      US 1998-75258P      A2 19980219
                                            WO 1999-US3171      W  19990212
                                            US 2000-595682      A1 20000616
REFERENCE COUNT:          9      THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
                                 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25  ANSWER 7 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1999:277438  CAPLUS
DOCUMENT NUMBER:          131:97098
TITLE:                    Comparison of activation of CPT-11 by rabbit and human
                          carboxylesterases for use in enzyme/prodrug therapy
AUTHOR(S):                Danks, Mary K.; Morton, Christopher L.; Krull, Erik
                          J.; Cheshire, Pamela J.; Richmond, Lois B.; Naeve,
                          Clayton W.; Pawlik, Cynthia A.; Houghton, Peter J.;
                          Potter, Philip M.
CORPORATE SOURCE:         Department of Molecular Pharmacology [M. K. D., C. L.
                          M., E. J. K., P. J., St. Jude Children's Research
                          Hospital, Memphis, TN, 38105, USA
SOURCE:                   Clinical Cancer Research (1999), 5(4), 917-924
                          CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER:                American Association for Cancer Research
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          31     THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
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RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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---Logging off of STN---


=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                10.04      46.70

STN INTERNATIONAL LOGOFF AT 08:57:41 ON 14 SEP 2006
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